REMARKS

Reconsideration of the present application in view of the above amendments and the following remarks is respectfully requested. Claims 1-7 and 9-22 were pending, of which claims 14 and 15 were withdrawn from further consideration. Claims 1, 5, 16, 19, and 20 have been amended. Support for the language "physiologically acceptable" in claims 1, 5, 16 and 20 may be found at page 3, lines 6-9. Additional support for the amendments in claim 16 may be found at page 5, lines 10-19. Support for the amendments in claim 19 may be found at page 5, lines 10-14. No new matter has been added.

Formal Matters:

The title of the invention stands objected to as allegedly not descriptive. More specifically, the Examiner states that (a) EDTA is required by all claims, and (b) it is the presence of EDTA that distinguishes the claimed invention from the prior art.

While believing that the title proposed in the amendment filed August 15, 2003 is descriptive, to facilitate allowance, Applicants have amended the title to "USE OF EDTA IN STABILIZING GRANULOCYTE MACROPHAGE COLONY-STIMULATING FACTOR." Accordingly, Applicants respectfully submit that this ground of objection has been overcome.

Rejection Under 35 U.S.C. §112, Second Paragraph

Claim 19 stands rejected under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite. More specifically, the Action states that this claim recites the amounts of mannitol, sucrose and TRIS as masses only and not as concentrations.

Applicants thank the Examiner for noting the above informalities. Applicants have amended claim 19 by inserting "/ml" as suggested by the Examiner. Accordingly, Applicants respectfully submit that this ground of rejection has been overcome.

Rejection Under 35 U.S.C. § 103(a)

Claims 1-7 and 9 stand under 35 U.S.C. §103(a) as being unpatentable over the LEUKINE® Sargramostim product insert, in view of Chalmers, Manufacturing Chemist & Aerosol News (March 1978, cited by Applicants), and U.S. Patent Number 5,217,954 (Foster *et al.*), and in the case of claims 4-7, further in view of U.S. Patent Number 5,545,536 (Kaushansky *et al.*), for the reasons set forth in the previous Office Action (Paper No. 11 dated May 15, 2003). The Action deems unpersuasive the arguments in the previous response (filed on August 15, 2003) that no motivation to combine the cited references was present in prior art. The Action asserts that the motivation to combine the cited references may be found in the LEUKINE® Sargramostim product insert, which warns against administering benzyl alcohol to newborns. In addition, the Action asserts that the motivation to combine the cited references may also be found in Foster *et al.*, which describes the use of EDTA to stabilize a cytokine (*i.e.*, bFGF) preparation.

Applicants respectfully traverse this ground of rejection. Applicants submit that a *prima facie* case of obviousness has not been established by the Action: there is not sufficient motivation for one of ordinary skill in the art to combine the cited references. The warning against administering benzyl alcohol to neonates in the LEUKINE® Sargramostim product insert does not provide the necessary motivation for substituting benzyl alcohol with EDTA in a GM-CSF formulation. First, the product insert describes not only LEUKINE formulations that contain benzyl alcohol, but also a LEUKINE formulation that does not contain benzyl alcohol. More specifically, the product insert describes that lyophilized LEUKINE may be constituted with 1 mL sterile water for injection (*see*, the second paragraph on page 1 of the insert). Thus, one of ordinary skill in the art, in view of the insert as a whole, would use lyophilized LEUKINE reconstituted in sterile water for administering to neonates. Such an approach would avoid significant time and efforts required for developing a new formulation.

Even assuming for the sake of argument that one is motivated to substitute benzyl alcohol with another antimicrobial preservative for administering GM-CSF in neonates, EDTA would not be an obvious choice. Generally a substance must meet the requirements of

appropriate regulatory guidelines regarding Antimicrobial Effectiveness Testing (AET) and Preservative Effectiveness Testing (PET) to be considered for use as a preservative. There is no evidence in the art that EDTA meets such requirements. Furthermore, many other antimicrobial preservatives (*e.g.*, phenol) have been used in the industry, some of which are suitable for administering to neonates. Accordingly, if one of ordinary skill in the art were to replace benzyl alcohol, such a person would choose a substance known to be suitable for administrating to neonates as a preservative instead of EDTA.

Applicants further submit that the Foster *et al.* reference also fails to provide the necessary motivation for using EDTA to stabilize GM-CSF. That both bFGF and GM-CSF are cytokines is insufficient for motivating one of ordinary skill in the art to stabilize GM-CSF with EDTA. The term "cytokine," as known in the art, refers to extracellular signal protein or peptide that acts as a local mediator in cell-cell communication (*see*, *Molecular Biology of The Cell*, 4th Ed. Alberts *et al.*, ed., published Garland Science, 2002, p. G:10, copy enclosed). It encompasses a diverse group of proteins and peptides with different amino acid sequences and functions. In fact, bFGF and GM-CSF are unrelated in their amino acid sequences: They only share about 10% sequence identity. As one of ordinary skill in the art would appreciate that a primary factor that determines the level of protein degradation is the amino acid sequence of the protein of interest. Accordingly, Applicants believe that such a person, in view of the sequence differences between bFGF and GM-CSF, would not have been motivated to use EDTA to stabilize GM-CSF.

Even assuming for the sake of argument that a *prima facie* case of obviousness has been established, Applicants respectfully submit that such a *prima facie* case of obviousness can be rebutted by the unexpected results disclosed in the present application. For instance, Examples 2 and 3 show that EDTA reduces N-terminal degradation of GM-CSF. Such results are unexpected in view of the cited references. None of the cited references suggest that the claimed GM-CSF formulation would have no, or a reduced level of, N-terminal degradation. The Foster *et al.* reference only discloses that EDTA may reduce the oxidation or metal-induced

In view of the above remarks, Applicants submit that this ground of rejection under 35 U.S.C. § 103(a) has been overcome. Withdrawal of this rejection is respectfully requested.

Claims 10-13 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over the LEUKINE® Sargramostim product insert, Chalmers, Foster, and further in view of U.S. Patent Number 6,500,418 B1 (Dieckgraefe *et al.*) for reasons set forth in the previous Office Action (Paper No 11).

Applicants respectfully traverse this ground of rejection. As discussed above, the composition of claim 1 is not obvious in view of the LEUKINE® Sargramostim product insert, Chalmers, and Foster for failing to provide the necessary motivation for using EDTA to stabilize GM-CSF. Such a deficiency has not been remedied by the Dieckgraefe *et al.* reference. More specifically, the Dieckgraefe *et al.* reference relates to the use of GM-CSF in treating inflammatory bowel disease. It does not suggest or teach the use of EDTA in stabilizing GM-CSF. Thus, Applicants submit that the methods of using the composition of claim 1, as recited in claims 10-13, would not be deemed obvious in light of the Dieckgraefe *et al.* reference.

In view of the above remarks, Applicants submit that this ground of rejection has been overcome. Withdrawal of this rejection is respectfully requested.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

All of the claims remaining in the application are believed to be allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

Respectfully submitted,

SEED Intellectual Property Law Group PLLC

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QXL:jab

Enclosures:
Postcard
Copy of *Molecular Biology of The Cell*, 4th Ed. Alberts *et al.*, ed., published Garland Science, 2002, p. G:10

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